Comparison of the efficacy and safety of LBAL, a candidate adalimumab biosimilar, and adalimumab reference product in patients with active rheumatoid arthritis inadequately responding to methotrexate: A 52-week phase III randomised study

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Abstract

Objective

To evaluate the similarities between LBAL (adalimumab biosimilar candidate) and the adalimumab reference product (ADL) in terms of efficacy and safety, including immunogenicity, in patients with active rheumatoid arthritis despite methotrexate treatment.

Methods

This phase III, multicentre, randomised, double-blind, parallel-group, 56-week study was conducted in Japan and Korea. During the first 24 weeks, patients subcutaneously received 40 mg of LBAL or ADL every two weeks (LBAL and ADL groups). During the subsequent 28 weeks, the LBAL group patients and half of the ADL group patients received LBAL (L-L and A-L arms). The remaining ADL group patients continued to receive ADL (A-A arm). The primary efficacy endpoint was the change from baseline in disease activity score 28-erythrocyte sedimentation rate (DAS28-ESR) at Week 24. American College of Rheumatology (ACR) response rates, adverse events (AEs), and anti-drug antibody (ADA) were also assessed.

Results

In total, 383 patients were randomised. The least squares (LS) mean changes from baseline in DAS28-ESR at Week 24 were -2.45 and -2.53 in the LBAL (n=191) and ADL (n=190) groups, respectively. The 95% confidence interval (CI; -0.139, 0.304) of the difference (0.08) was within the pre-specified equivalence margin (-0.6, 0.6). Up to Week 52, the decreases in DAS28-ESR were maintained in all three arms. No notable differences in ACR20/50/70 were observed. The AE and ADA incidences were comparable between the arms.

Conclusion

LBAL was equivalent in efficacy and comparable in safety, including immunogenicity, to ADL. Switching from ADL to LBAL did not impact on efficacy and safety.

Key words

adalimumab, biosimilar pharmaceuticals, clinical trial, arthritis, rheumatoid

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Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disorder, causing pain, deformity, and reduced quality of life (QOL) (1, 2). As the general age of onset of RA is 20–40 years (3), RA symptoms and sequelae can affect an individual's work productivity.

Currently, recommended medicinal treatment approaches for RA (4) are generally classified into conventional synthetic disease-modifying anti-rheumatic drugs (*e.g.* methotrexate [MTX]), biological disease-modifying anti-rheumatic drugs (bDMARDs) (*e.g.* tumour necrosis factor [TNF] inhibitors, interleukin-6 inhibitors, and T-cell co-stimulation inhibitors) and targeted synthetic disease-modifying anti-rheumatic drugs. Adalimumab (ADL; brand name Humira®, AbbVie) is a bDMARD that inhibits TNF in joints (5).

Biological DMARDs are highly effective in improving physical function, QOL, and work capacity (4). Owing to increased demand for bDMARDs, many biosimilars, comparable to originator bDMARDs in efficacy and safety, are available (6, 7); these include a product we developed, LBEC0101, a biosimilar of etanercept (8, 9). Here, we report the results of a phase III study of LBAL, a biosimilar candidate of the commonly used drug adalimumab (ADL) (10). LBAL had similar pharmacodynamic properties to ADL in non-clinical studies and was equivalent in pharmacokinetics (PK) to ADL in a phase I study, without remarkable differences in tolerability or immunogenicity (11). This phase III study compared efficacy and safety, including immunogenicity, of LBAL versus ADL in patients with active RA inadequately responding to MTX.

Materials and methods

Study design

This multicentre, randomised, double-blind, parallel-group, active-controlled, 56-week study (ClinicalTrials.gov NCT02746380) was conducted at 64 and 32 sites in Japan and Korea, respectively.

The study comprised a 52-week treatment period (24 weeks of Period I and 28 weeks of Period II) and a 4-week post-treatment follow-up period (Fig. 1). After screening, patients were randomly assigned to treatment using a Web Response System. Allocation was performed centrally by stratified randomised block design within each stratum of allocation by country (Japan or Korea) and previous bDMARD use (yes or no). Both study drugs were provided in 40 mg/0.8 mL syringes containing clear injectable liquid. Packaging, including the syringe, blister, and study drug box and labelling, was identical and double-blinded. Investigators, patients, and study sponsors were all blinded to the study drug throughout the study. The randomisation list was not available at the study site, to the study monitors, or any of the sponsors' study teams. Unblinding was not to occur except in emergency situations.

Eligible patients were assigned to one of three arms (L-L, A-L, and A-A arms) at a ratio of 2:1:1. During Period I, the L-L arm received LBAL, and A-L and A-A arms received ADL (namely, LBAL group and ADL group, respectively) to compare the efficacy and safety of LBAL and ADL. During Period II, the L-L arm and A-A arm continued to receive LBAL and ADL to evaluate the efficacy and safety of continuous LBAL or ADL. The A-L arm received LBAL to evaluate switching from ADL to LBAL.

This study was conducted according to the Declaration of Helsinki, International Committee on Harmonisation Good Clinical Practice guideline, and applicable local laws and regulations. The protocol was approved by the regulatory authorities in each country and by the ethics committees of each study centre.

Patients

Eligibility criteria were age 20–75 years; active RA diagnosis according to the active RA criteria for ≥3 months and the 1987 revised American College of Rheumatology (ACR) classification criteria (12); inadequate response to MTX administered for ≥12 weeks; and treatment with a stable MTX dose for ≥4 weeks. Exclusion criteria were active tuberculosis or untreated latent tuberculosis, previous ADL treatment,

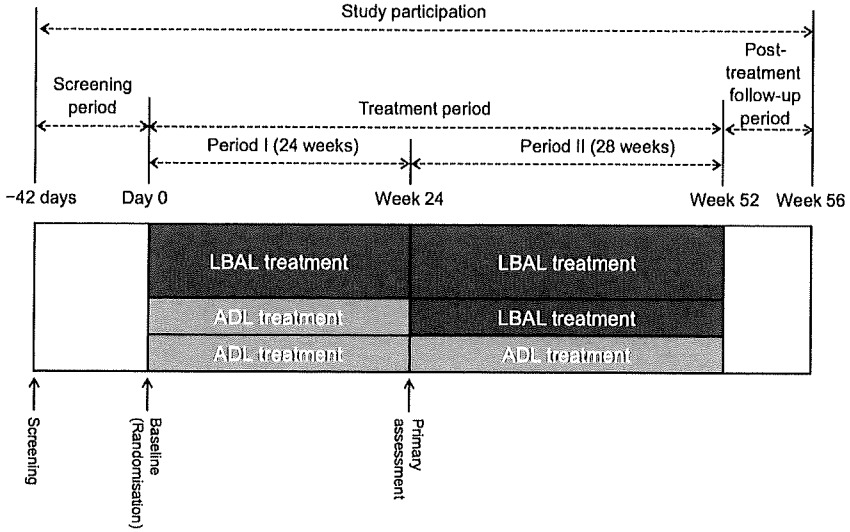

Fig. 1. Study design. ADL: adalimumab reference product.

treatment with ≥2 bDMARDs, leflunomide treatment within 12 weeks before the first administration of study drugs, treatment with JAK inhibitors within 16 weeks before the first administration of the study drugs, or other non-bDMARD treatment within four weeks before the first administration of study drugs.

Treatment

LBAL and ADL were administered as 40 mg/0.8 ml subcutaneous injections every two weeks. Patients continued a stable MTX dose within the approved dosage in Japan and Korea; however, MTX dose reduction was allowed for safety at the investigator's discretion. Supplementary Text S1 (in the online Supplementary file) lists the prohibited and restricted concomitant medications.

Endpoints

The primary endpoint was change from baseline in disease activity score 28-erythrocyte sedimentation rate (DAS28-ESR) at Week 24. Secondary endpoints were changes from baseline in DAS28-ESR at Weeks 12 and 52; the proportion of patients with an improvement of 20% [ACR20], 50% [ACR50], and 70% [ACR70] by ACR criteria (13); European League Against Rheumatism (EULAR) response (14); low activity (DAS28-ESR ≤3.2) rates; remission rates (DAS28-ESR <2.6); and change from baseline in DAS28-C-reactive protein (CRP) at Weeks 12, 24, and 52.

Incidences of adverse events (AEs) (per Medical Dictionary for Regulatory Activities, version 20), adverse drug reactions (ADRs), and AEs of special interest (*i.e.* infections, tuberculosis, allergic reaction, interstitial lung disease, lupus erythematosus, demyelinating disorders, heart failure, hematologic disorders, hepatic function disorder, malignancies, hepatitis B reactivation, psoriasis, sarcoidosis, and injection site reaction) were assessed.

PK was assessed by measuring trough concentration (C_{trough}) at Weeks 12, 24, and 52. To determine immunogenicity, anti-drug antibody (ADA) and neutralising antibody (nAb) were measured at Weeks 0, 12, 24, and 52 by validated electrochemiluminescent immunoassays using biotinylated LBAL and SULFO-TAG labelled LBAL for ADA and biotinylated LBAL and SULFO-TAG labelled TNF-α for nAb. If the ADA test was positive, nAb was then determined. PK and immunogenicity were assessed at central laboratories.

Comparisons were made between the LBAL and ADL groups for Period I data. Period II data were assessed between the L-L, A-L, and A-A arms.

Statistical analysis

Sample size calculations were based on the standard deviation (SD) of the change from baseline in DAS28 of 1.6 in the previous ADL study (15). Both LBAL and ADL treatments were expected to achieve identical changes from baseline in DAS28. A sample size of 372 was estimated to yield a statistical power of 90% for the two-sided 95% confidence interval (CI) of the difference between the groups to an equivalence margin of -0.6, 0.6, which is considered clinically significant based on EULAR criteria (14). The target sample size was 380 patients to account for a 2% withdrawal rate: L-L, 190 patients; A-L, 95 patients; and A-A, 95 patients.

The primary efficacy endpoint was analysed using the full analysis set (FAS) data. The sensitivity of FAS results was verified using the per-protocol set (PPS). The safety analysis was conducted on the safety set and the PK analysis on the PK set. Analysis set definitions are detailed in Supplementary Text S2.

For primary endpoints, point estimates of the treatment difference between LBAL and ADL groups and 95% CIs of the DAS28-ESR change at Week 24 were derived using the analysis of covariance adjusted for country, previous use of a bDMARD and DAS28-ESR at baseline. The CIs were assessed according to the pre-specified margin of equivalence (-0.6, 0.6).

Missing data at baseline were not replaced in any analyses, but the last observation carried forward method was employed for any missing data at post-baseline visits (FAS analyses). In calculating response rates for the FAS, subjects who prematurely withdrew from the study prior to the given time point or who had a missing assessment at the given time point were considered as having no response regardless of the reason for withdrawal. Data for safety and PK variables were summarised, using descriptive statistics, and missing data were not imputed. The analysis was performed using SAS v. 9.3 (SAS Institute Inc., Cary, North Carolina, USA).

Results

Patient disposition and baseline characteristics

Of the 469 patients screened, 383 were randomised to the L-L (n=192), A-L

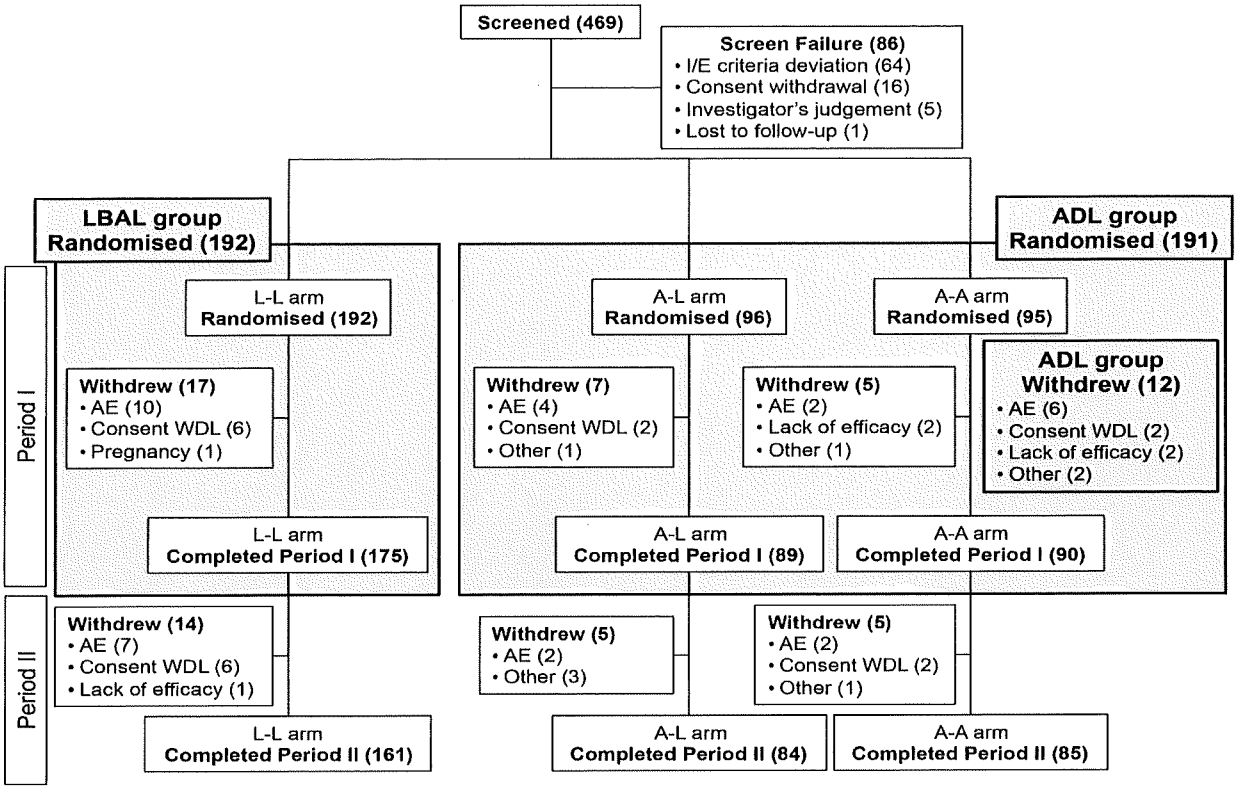

Fig. 2. Patient disposition.
A: adalimumab reference product; ADL: adalimumab reference product; AE: adverse event; I/E: Inclusion/Exclusion; L: LBAL; WDL: withdrawal.

(n=96), and A-A (n=95) arms at baseline. Thus, the LBAL and ADL groups for Period I comprised 192 and 191 patients, respectively (Fig. 2).

In Period I, withdrawal rates were 8.9% (17/192) and 6.3% (12/191) in the LBAL and ADL groups, respectively, without notable differences between groups. The withdrawal rates in Period II were comparable among the three arms (L-L, 7.3% [14/175]; A-L, 5.2% [5/89]; A-A, 5.3% [5/90]), and many withdrawals were due to AEs.

Of the 383 randomised patients, 381 were included in the FAS (L-L, n=191; A-L, n=96; A-A, n=94), as two patients failed to complete the post-baseline DAS28-ESR assessment. Patient demographics and baseline characteristics were well balanced among the groups (Table I) and arms (Suppl. Table S1).

Efficacy

– Efficacy at Week 24

LS mean changes from baseline in DAS28-ESR at Week 24 in the FAS (primary endpoint) were -2.45 (95% CI: -2.631, -2.266) in the LBAL group and -2.53 (95% CI: -2.708, -2.355) in the ADL group (Fig. 3A). LBAL showed equivalent efficacy to ADL as the mean treatment difference was 0.08, with a 95% CI of -0.139, 0.304, which was within the pre-specified equivalence margin (-0.6, 0.6). A similar result was observed in the PPS (difference: 0.11, 95% CI: -0.101, 0.325). Subgroup analysis demonstrated the comparability of LBAL and ADL, regardless of age, sex, previous bDMARD use, country, and DAS28-ESR and MTX dose (Suppl. Table S2).

Achieving ACR20 response at Week 24 was an important secondary endpoint and was achieved by a comparable percentage of patients in the LBAL (83.8%) and ADL (85.3%) groups (Table II).

– Efficacy up to Week 52

The continuous LBAL and ADL treatments (L-L and A-A arms) similarly decreased DAS28-ESR up to Week 52 (Fig. 3B). A comparable decrease was observed in the A-L arm after ADL was switched to LBAL at Week 24, suggesting that efficacy was maintained irrespective of switching.

No notable differences in ACR20/50/70 response rates were seen among treatment arms from Week 12 to 52 (Fig. 4). Similar trends were observed for patients with low disease activity or remission by DAS28-ESR (Suppl. Table S3), good or moderate EULAR response (Suppl. Table S4) and the change in DAS28-CRP (Suppl. Fig. S1).

Safety

– Safety up to Week 24

In the LBAL and ADL groups, 68.2% and 71.2% of patients experienced AEs, and 39.1% and 37.7% experienced ADRs, respectively. Thus, the incidences of AEs and ADRs up to Week 24 were similar between the groups.

– Safety up to Week 56

In the L-L, A-L, and A-A arms, incidences of AEs up to Week 56 were similar among the three arms (AEs: 81.3%, 88.5%, and 85.3% and ADRs, 49.0%, 47.9%, and 46.3%), respectively (Table III). No notable differences in inci-

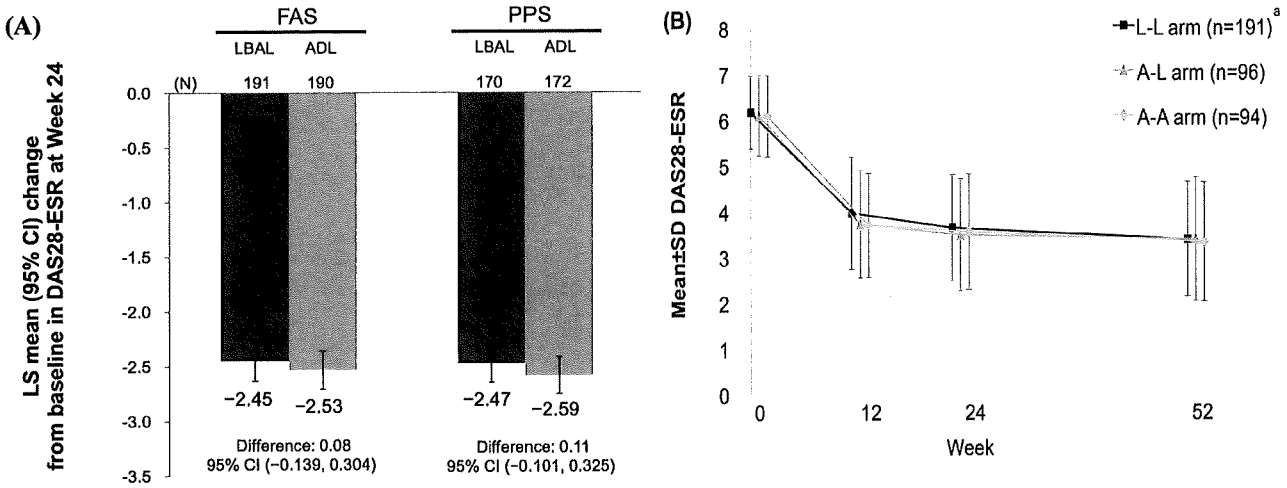

Fig. 3. **A**: LS mean change from baseline in DAS28-ESR at Week 24.
B: mean DAS28-ESR at baseline, Week 12, Week 24, and Week 52 (full analysis set).
[a]DAS28-ESR score from one patient was excluded at Week 12. Error bars show ± SD.
ADL: adalimumab reference product; CI: confidence interval; DAS: disease activity score; ESR: erythrocyte sedimentation rate; FAS: full analysis set; LS: least squares; PPS: per-protocol set; SD: standard deviation.

Table I. Demographics and clinical characteristics by treatment group (full analysis set).

Variable	LBAL group n=191	ADL group n=190	Overall n=381
Age, years	55.2 ± 12.1	54.0 ± 11.0	54.6 ± 11.5
Sex, female	161 (84.3)	162 (85.3)	323 (84.8)
Ethnicity, Asian	191 (100.0)	190 (100.0)	381 (100.0)
Weight, kg	57.5 ± 11.0	57.4 ± 11.4	57.5 ± 11.2
Functional status in RA			
I	32 (16.8)	29 (15.3)	61 (16.0)
II	130 (68.1)	140 (73.7)	270 (70.9)
III	29 (15.2)	21 (11.1)	50 (13.1)
IV	0 (0.0)	0 (0.0)	0 (0.0)
Duration since RA diagnosis, years	7.2 ± 8.2	7.5 ± 7.2	7.3 ± 7.7
Rheumatoid factor positivity	152 (79.6)	153 (80.5)	305 (80.1)
Tender joint count from 68 joints	14.8 ± 7.9	16.3 ± 10.3	15.5 ± 9.2
Tender joint count from 28 joints	10.4 ± 5.3	10.5 ± 5.8	10.4 ± 5.6
Swollen joint count from 66 joints	11.8 ± 6.0	12.0 ± 6.8	11.9 ± 6.4
Swollen joint count from 28 joints	8.8 ± 4.2	8.6 ± 4.6	8.7 ± 4.4
DAS28-ESR	6.2 ± 0.8	6.1 ± 0.9	6.1 ± 0.8
ESR, mm/hour	55.8 ± 25.3	52.5 ± 22.7	54.2 ± 24.1
CRP, mg/dL	2.2 ± 3.0	1.5 ± 1.7	1.9 ± 2.5
MTX dose, mg/week	11.4 ± 3.0	11.4 ± 2.9	11.4 ± 3.0
HAQ-DI	1.3 ± 0.7	1.2 ± 0.7	1.2 ± 0.7
PtAP, mm	61.9 ± 22.6	61.4 ± 23.7	61.6 ± 23.1
PtGADA, mm	61.8 ± 21.1	59.7 ± 23.3	60.7 ± 22.2
PhGADA, mm	61.9 ± 18.0	60.5 ± 18.5	61.2 ± 18.2
Patients who used bDMARDs previously	34 (17.8)	42 (22.1)	76 (19.9)
Patients who used corticosteroids at baseline	121 (63.4)	127 (66.8)	248 (65.1)

Data are presented as mean ± SD or n (%).
ADL: adalimumab reference product; bDMARD: biological disease-modifying anti-rheumatic drug; DAS: disease activity score; ESR: erythrocyte sedimentation rate; MTX: methotrexate; PhGADA: physician's global assessment of disease activity; PtAP: patient's assessment of pain; PtGADA: patient's global assessment of disease activity; RA: rheumatoid arthritis; SD: standard deviation.

dences of AEs and ADRs between the A-L and A-A arms, either during the overall study or in Period II, suggests that switching did not lead to increases in AEs or ADRs.

SAEs were reported in 17.7%, 8.3%, and 8.4% of patients in the L-L, A-L, and A-A arms, respectively. The variation in SAE incidence between the L-L (17.7%) and the A-A arms (8.4%) was mainly due to differences in the number of serious infections (L-L, 7.8% [15 patients, 18 events]; A-A, 0%) (Table III). Of 18 serious infection cases in the L-L arm, three events (pneumonia, peritoneal tuberculosis, and urinary tract infection) occurred in two patients each, and the remaining 12 events occurred in one patient each (Suppl. Table S5). Almost all the serious infections in the L-L arm had been previously reported, except for a post-procedural infection, which occurred after sequestrectomy for osteomyelitis. All SAEs were resolved or recovering by the end of the study. The A-L and A-A arms had comparable SAE incidences overall and in Period II.

There were no notable differences in type and incidence of the most frequent AEs (>5%) among the three arms (Table IV). In the A-L arm, no AEs increased in frequency after switching. Of the AEs that occurred during Period I, none were exacerbated during Period II.

Incidences of AEs of special interest are also shown in Table IV and Supplementary Table S6. Regarding infections, there were no significant differences in incidence among the three arms. Although tuberculosis was re-

Table II. Response rates based on the ACR improvement response criteria at Week 24 (full analysis set).

		n	Response rate % (n)	Response rate difference relative to ADL (95% CI)
ACR20	LBAL group	191	83.8 (160)	-1.5 (-8.8 – 5.8)
	ADL group	190	85.3 (162)	
ACR50	LBAL group	191	58.1 (111)	-10.8 (-20.4 – -1.2)
	ADL group	190	68.9 (131)	
ACR70	LBAL group	191	33.0 (63)	-8.6 (-18.3 – 1.1)
	ADL group	190	41.6 (79)	

ACR: American College of Rheumatology; ADL: adalimumab reference product; CI: confidence interval.

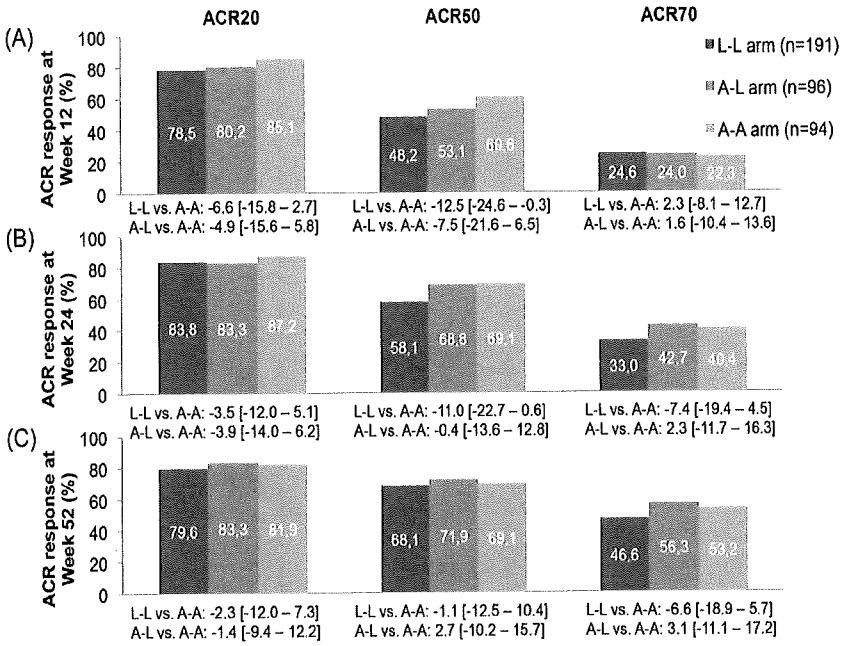

Fig. 4. Response rates based on the ACR improvement response criteria at (**A**) Week 12, (**B**) Week 24 and (**C**) Week 52 (full analysis set)
A: adalimumab reference product; ACR: American College of Rheumatology; ADL: adalimumab reference product; L: LBAL.
Below each figure panel, we show the difference in response rate between arms L-L *vs.* A-A and A-L *vs.* A-A and the corresponding 95% confidence intervals in ACR20, ACR50 and ACR70.

ported in nine patients, three had clinical symptoms and the other six patients had a positive interferon-γ test without symptoms (data not shown). Malignancies, one case of lung adenocarcinoma (L-L arm) and one of lymphoproliferative disorder (A-L arm), were recovering at the end of the study. There was no significant difference in the incidence of injection site reactions between the L-L (4.2%) and A-A (6.3%) arms. Switching did not seem to affect the occurrence of injection site reactions, despite the slightly higher incidence (13.5%) observed in the A-L arm, because most of the patients (12.5%) experienced injection site reactions with ADL administration in Period I, and the incidence in the A-L arm in Period II (4.2%) was similar to that in the A-A arm (3.2%).

Immunogenicity

Overall, 8.3% (L-L), 11.5% (A-L), and 8.4% (A-A) of patients had at least one positive ADA test during the study (Suppl. Table S7). Additionally, 7.8% of patients in the L-L arm, 10.4% in the A-L arm, and 8.4% in the A-A arm had at least one positive nAb test. Incidences of ADA and nAb were similar among the three arms. ADA and nAb newly developed in 2.1% and 1.0% of patients in the A-L arm and in 1.1% and 1.1% of patients in the A-A arm, respectively, during Period II, indicating that switching did not affect the emergences of ADA and nAb.

The effects of ADA on PK, efficacy, and safety were assessed in the L-L and A-A arms without any notable differences between arms. Most of the ADA-positive patients had C_{trough} values below the lower limit of the 95% CI of the geometric mean of C_{trough} values in the ADA-negative patients (data not shown). Consistent with this, a higher rate of patients achieved a change from baseline in DAS28-ESR ≤0.6, which is categorized as "non-response" regardless of postdose disease activity based on EULAR criteria, and the rate of ACR20 responders among ADA-positive patients was lower than that among ADA-negative patients (Suppl. Table S8). In terms of safety, no significant differences were observed in the incidence of AEs or ADRs between the ADA-positive and ADA-negative patients (Suppl. Table S9). Injection site reactions are known as common ADA-related AEs (15-18); both ADA-positive patients and ADA-negative patients developed injection site reactions, but no clear relationship with ADA was observed [data not shown].

Discussion

This study evaluated the equivalence in efficacy of LBAL to ADL and assessed their safety profiles, including immunogenicity, for similarities. These data provide valuable information on switching from ADL to LBAL, which can be referred to when the originator product is switched to its biosimilar in clinical practice (19). A key aspect of this study was that DAS28-ESR was used as the primary endpoint instead of ACR20. Although ACR20 was used in many previous ADL biosimilar studies (20-23), DAS28-ESR is a continuous variable and, thus, is considered more sensitive for detecting potential treatment differences than a binary variable, as per the guidance document issued by the US Food and Drug Administration,

Table III. Overview of adverse events (safety set).

	Period I (Baseline to Week 24)		Period II (Week 24 to Week 52)			Overall (Baseline to Week 56)		
	LBAL group (n=192) % (n)	ADL group (n=191) % (n)	L-L arm (n=192) % (n)	A-L arm (n=96) % (n)	A-A arm (n=95) % (n)	L-L arm (n=192) % (n)	A-L arm (n=96) % (n)	A-A arm (n=95) % (n)
Any AE	68.2 (131)	71.2 (136)	52.1 (100)	53.1 (51)	61.1 (58)	81.3 (156)	88.5 (85)	85.3 (81)
Any ADR	39.1 (75)	37.7 (72)	24.5 (47)	24.0 (23)	25.3 (24)	49.0 (94)	47.9 (46)	46.3 (44)
Any SAE	8.3 (16)	4.7 (9)	8.9 (17)	4.2 (4)	3.2 (3)	17.7 (34)	8.3 (8)	8.4 (8)
Serious infection	4.2 (8)	1.0 (2)	3.1 (6)	2.1 (2)	0	7.8 (15)	4.2 (4)	0
Any AE leading to discontinuation	6.3 (12)	4.7 (9)	2.6 (5)	1.0 (1)	0	8.9 (17)	6.3 (6)	4.2 (4)
Deaths	0	0	0	0	0	0	0	0

A: adalimumab reference product; ADL: adalimumab reference product; ADR: adverse drug reaction; AE: adverse event; L: LBAL; SAE: serious adverse event.

Table IV. Adverse events reported in >5% of patients by preferred term in each treatment arm and adverse events of special interest (safety set).

Overall (Baseline to Week 56)	L-L arm (n=192) % (n)	A-L arm (n=96) % (n)	A-A arm (n=95) % (n)
AE reported in >5% of patients			
Viral upper respiratory tract infection	19.3 (37)	25.0 (24)	28.4 (27)
Cough	6.3 (12)	4.2 (4)	8.4 (8)
Rash	6.3 (12)	3.1 (3)	0
Upper respiratory tract infection	5.7 (11)	5.2 (5)	3.2 (3)
Diarrhoea	5.2 (10)	1.0 (1)	2.1 (2)
Rheumatoid arthritis [a]	4.7 (9)	5.2 (5)	5.3 (5)
Hepatic enzyme increased	3.1 (6)	6.3 (6)	4.2 (4)
Herpes zoster	2.6 (5)	5.2 (5)	2.1 (2)
Arthralgia	2.1 (4)	1.0 (1)	5.3 (5)
Headache	0.5 (1)	6.3 (6)	2.1 (2)
Injection site erythema	0.5 (1)	6.3 (6)	4.2 (4)
Any AESIs	58.9 (113)	58.3 (56)	56.8 (54)
Infections (serious, non-serious, overall)	45.8 (88)	46.9 (45)	47.4 (45)
Allergic reaction	9.9 (19)	6.3 (6)	6.3 (6)
Hepatic function disorder	6.3 (12)	0	5.3 (5)
Injection site reactions	4.2 (8)	13.5 (13)	6.3 (6)
Tuberculosis	4.2 (8)	1.0 (1)	0
Interstitial lung disease	2.6 (5)	1.0 (1)	1.1 (1)
Heart failure	1.0 (2)	1.0 (1)	3.2 (3)
Psoriasis	1.0 (2)	0	0
Blood disorder	0.5 (1)	1.0 (1)	0
Malignancies	0.5 (1)	1.0 (1)	0
Lupus erythematosus	0	1.0 (1)	0
Demyelinating disorders:	0	0	0
Hepatitis B reactivation	0	0	0
Sarcoidosis	0	0	0

A: adalimumab reference product; AE: adverse event; AESI: adverse events of special interest; L: LBAL.
[a] Rheumatoid arthritis indicates rheumatoid arthritis flare.

"Rheumatoid Arthritis: Developing Drug Products for Treatment" (13, 24, 25).

In this study, the equivalence of LBAL to ADL in terms of efficacy was demonstrated with mean changes in DAS28-ESR; values were similar to those in other ADL biosimilar studies with a comparable study design (21, 23). Although an equivalence margin for ACR20 was not predefined in this study, the between-group difference in ACR20 (-1.5% [95% CI: -8.8, 5.8]) was within the equivalence margin (approximately ±13%) defined in other ADL biosimilar studies, which supports the equivalence of LBAL with ADL in terms of efficacy (20-23). The results of this study show the comparability between both investigational drugs and indicate that it was appropriately evaluated using the equivalence margin, which is stricter than the non-inferiority margin.

The results of AEs and ADRs, including deaths, AEs of special interest, and the most frequent AEs observed, suggested that the safety profiles of LBAL and ADL are similar.

Although infection is known as the most common AE with ADL (26), no notable differences were observed in the incidence and type of AEs among the arms. Further, infection-related AEs were similar to those previously reported for ADL or other ADL biosimilars (16, 17, 20-22). In this study, the incidences of serious infections were 7.8%, 4.2%, and 0% in the L-L, A-L, and A-A arms, respectively. To clarify whether LBAL treatment was related to the occurrence of serious infection, we analysed patient background characteristics that may predispose these patients to serious infections using five risk factors identified in a previous Japanese post-marketing surveillance of the originator, such as concomitant pulmonary disease and high dose of MTX (27). Although no statistical significance was reached, the L-L arm tended to include a higher number of patients with concomitant pulmonary disease and patients with concomitance of corticosteroids at doses >5 mg/day compared with the A-A arm. More patients in the A-L arm tended to concomitantly have pulmonary disease compared with the A-A arm (Suppl. Table S10). Thus, the arm with more risk factors at baseline tended to have more serious infections during the study.

Moreover, in the A-L arm, two patients each in Period I (ADL-treatment period) and Period II (LBAL-treatment period) developed serious infections, suggesting that LBAL did not lead to more serious infections compared with ADL in the same population. Differences in the incidence of serious infections could be attributed to slight variations in risk factors among the arms.

Considering that the incidence of serious infections during 1-year treatment varied widely, ranging from 0 to 5.3% in previous ADL originator or ADL biosimilar studies (16, 22), the serious infection incidence range observed in this study (0 to 7.8%) could be within the acceptable range. Additionally, based on the incidences of 2.6% in the TNF inhibitors administration group and 2.0% in the control group, including placebo reported in another study, the incidence of 0% in the L-L arm in this study was thought to have occurred accidentally (28). Except for one post-procedural infection, the serious infections observed in this study were described previously with the ADL originator. Therefore, no new safety concerns were raised in this study, and LBAL did not seem to be associated with a higher risk of infections or serious infections than what has been reported for the originator in the clinical setting.

The observed ADA incidences were comparable between the arms. The impact of ADA on lower C_{trough} and lower efficacy in ADA-positive patients was consistent with previous ADL findings (29-31). No impact of the switching was observed in efficacy, safety, PK, or immunogenicity. These results were consistent with the findings of other biosimilar studies (7, 32, 33).

A major limitation of this study was the inclusion of Asian patients only, which could limit the generalisability of the results to other ethnicities. However, as the originator is known to be insensitive to both intrinsic and extrinsic ethnic factors, LBAL is also expected to show similarity with the originator in other populations. The relatively small number of patients who received LBAL is another potential limitation. The risk factors for serious infections suggested by this study could be further explored in post-marketing surveillance, with a larger population.

In conclusion, LBAL was equivalent to ADL in efficacy and had a comparable safety profile in patients with RA. Long-term efficacy and safety were also comparable among the three arms during the 52-week treatment period. No concerns were raised after switching from ADL to LBAL in terms of efficacy and safety.

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